Obstructive Sleep Apnea in Young Lean Men

Impact on insulin sensitivity and secretion

Sushmita Pamidi, MD[1]
Kristen Wroblewski, MSC[2]
Josiane Broussard, PHD[1]
Andrew Day, BSC[1]
Erin C. Hanlon, PHD[1]
Varghese Abraham, MD[1]
Esra Tasali, MD[1]

OBJECTIVE—To assess whether the presence of obstructive sleep apnea (OSA) affects glucose metabolism in young, lean individuals who are healthy and free of cardiometabolic disease.

RESEARCH DESIGN AND METHODS—In a prospective design, 52 healthy men (age 18–30 years; BMI 18–25 kg/m^2) underwent laboratory polysomnogram followed by a morning oral glucose tolerance test (OGTT). We stratified all subjects according to the presence or absence of ethnicity-based diabetes risk and family history of diabetes. We then used a frequency-matching approach and randomly selected individuals without OSA, yielding a total of 20 control men without OSA and 12 men with OSA. Indices of glucose tolerance, insulin sensitivity, and insulin secretion (early phase and total) were compared between men with OSA and control subjects. The incremental areas under the glucose (incAUC$_{glu}$) and insulin (incAUC$_{ins}$) curves were calculated using the trapezoidal method from 0 to 120 min during the OGTT.

RESULTS—Men with OSA and control subjects were similar in terms of age, BMI, ethnicity-based diabetes risk, family history of diabetes, and level of exercise. Both groups had normal systolic and diastolic blood pressure and fasting lipid levels. After ingestion of a glucose load, men with OSA had 27% lower insulin sensitivity (estimated by Matsuda index) and 37% higher total insulin secretion (incAUC$_{ins}$) than the control subjects, despite comparable glucose levels (incAUC$_{glu}$).

CONCLUSIONS—In young, lean, and healthy men who are free of cardiometabolic disease, the presence of OSA is associated with insulin resistance and a compensatory rise in insulin secretion to maintain normal glucose tolerance. Thus, OSA may increase the risk of type 2 diabetes independently of traditional cardiometabolic risk factors.

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Obstructive sleep apnea (OSA) is a disorder characterized by repetitive episodes of upper-airway obstruction during sleep, which result in intermittent hypoxemia and transient arousals leading to sleep fragmentation and poor sleep quality. Obesity, male sex, and advancing age are the strongest risk factors for OSA (1). Notably, OSA is highly prevalent in overweight and obese individuals (2,3), who represent approximately two-thirds of the U.S. adult population today.

Increasing evidence from population-based and clinical studies suggests an association between OSA, insulin resistance, and type 2 diabetes in overweight and obese adults (4–7) even after statistical adjustments for age, adiposity, and other shared risk factors. In the few studies that have included individuals with a BMI <25 kg/m^2, the presence of OSA was found to be associated with insulin resistance in selected clinical populations of Asian origin (8–10) and with a higher prevalence of prediabetes in a subset of data obtained from the Sleep Heart Health Study, a multicenter cohort of community-dwelling adults in the U.S (11). However, these studies of lean individuals were conducted in middle-aged and older adults who had varying degrees of cardiovascular disease such as hypertension and dyslipidemia, as well as other potential comorbidities. Thus, it is still unclear whether the link between OSA and type 2 diabetes is independent of potential confounding effects of obesity and other cardiometabolic risk factors (12), which prevail both in OSA and in disorders of glucose metabolism.

We questioned whether the presence of OSA affects glucose metabolism in individuals who are otherwise healthy and free of cardiometabolic disease. To address this question, we assessed the response to oral glucose tolerance testing (OGTT) in healthy young lean men with and without OSA.

RESEARCH DESIGN AND METHODS

Healthy men aged 18–30 years and who had a BMI between 18 and 25 kg/m^2 were recruited from the local community in response to advertisements seeking healthy volunteers with no sleep complaints. We did not select subjects according to symptoms of OSA. Exclusion criteria were as follows: history of any chronic medical condition, any acute illness, shift work, travel across time zones during the past 4 weeks, depressed mood (as assessed by Center for Epidemiologic Studies of Depression score >16), use of any prescription or over-the-counter medications or supplements known to affect sleep or glucose metabolism, current smoking, significant alcohol or caffeine consumption, or abnormal findings on physical examination or routine laboratory testing. The institutional review board of the University of Chicago approved the protocol, and all participants gave written informed consent.

All participants underwent an overnight full laboratory polysomnography for assessment of the presence and severity of OSA. On the following morning, a standard 75-g OGTT was performed after an overnight fast, a 12-lead electrocardiogram was obtained, and a fasting blood sample was collected for routine laboratory tests including complete blood counts, comprehensive metabolic panel, thyroid function tests, lipid panel, and A1C.

From the [1]Department of Medicine, University of Chicago, Chicago, Illinois; and the [2]Department of Health Studies, University of Chicago, Chicago, Illinois.
Corresponding author: Sushmita Pamidi, sushmita.pamidi@mail.mcgill.ca.
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Polysomnography

Overnight laboratory polysomnography (Neurofax EEG 1100 system; Nihon Kohden, CA) was performed with bedtimes scheduled between 2300 and 2330 h and between 0730 and 0800 h. Polysomnographic recordings included electroencephalography, bilateral electrooculography, chin and leg electromyography, electrocardiography, airflow by nasal pressure transducer and oronasal thermistor, thoracic and abdominal respiratory efforts, and oxygen saturation by pulse oximetry. All sleep recordings were initially scored by the same registered polysomnographic technologist and then reviewed by a board-certified sleep medicine specialist. Sleep stages were visually scored in 30-s epochs as rapid eye movement (REM) sleep; non-REM sleep, i.e., stages N1, N2, and N3 (i.e., slow-wave sleep); and wake according to standard criteria (13). Respiratory events and microarousals were scored according to established criteria (13). The apnea-hypopnea index (AHI) was calculated as the total number of obstructive apneas and hypopneas per hour of sleep. Hypopneas were defined as a decrease in nasal pressure signal of ≥50% of baseline, which was associated with either a ≥3% desaturation or an arousal. OSA was defined as an AHI ≥5 events per hour. Oxygen desaturation index was calculated as the total number of ≥3% desaturations per hour of sleep. Arousal index was calculated as the total number of microarousals per hour of sleep.

OGTT

An antecubital intravenous catheter was inserted in the morning after an overnight fast. Baseline samples were obtained at −15 and 0 min for measurement of glucose and insulin concentrations. At time 0 min, 75 g glucose was ingested, and blood samples were collected for the measurement of glucose and insulin concentrations at 30, 60, 90, and 120 min. Plasma glucose was measured using a STAT-2300 analyzer (Yellow Springs). Serum insulin was measured by chemiluminescence assays using the Immulite immunochemistry system (Diagnostic Products, Los Angeles, CA). Fasting glucose and insulin concentrations were calculated as the average of the −15 and 0 min readings. The insulin sensitivity index was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) based on fasting glucose and insulin levels (14) and by the Matsuda index as previously described (15). Early-phase insulin secretion was estimated by the insulinogenic index based on the ratio between incremental insulin and glucose concentrations during the first 30 min of the OGTT ($I_{0–30}/G_{0–30}$) (16,17). The incremental areas under the glucose ($incAUC_{glu}$) and insulin ($incAUC_{ins}$) curves were calculated according to the trapezoidal rule between 0 and 120 min during the OGTT. The $incAUC_{ins}$ and $incAUC_{ins}/incAUC_{glu}$ were used as measures of total insulin secretion.

Statistical analysis

The main objective of this study was to examine the impact of OSA on glucose metabolism in a group of young and lean men. To this effect, participants were selected based on preset criteria for age (18–30 years) and BMI (18–25 kg/m^2). Next, we stratified all individuals (n = 52) according to two additional determinants of diabetes risk: ethnicity-based diabetes risk (classified as "high" for African Americans, Asians, and Hispanics and "low" for Caucasians) and family history of diabetes (classified as "yes" if at least one first-degree relative had type 2 diabetes and "no" if none of the first-degree relatives had type 2 diabetes). Finally, we used a frequency-matching approach and randomly selected twice as many individuals without OSA (i.e., control subjects) as there were individuals with OSA (i.e., case subjects) such that the distribution of control subjects across these four strata was the same (or as close as possible) as the distribution of case subjects. This frequency-matching approach yielded a total of 20 control men without OSA and 12 men with OSA.

Group data were expressed as means ± SEM. Group differences between men with OSA and control subjects were tested using two-sided t tests for continuous variables and χ^2 tests for categorical variables unless otherwise noted. Analyses were performed on log-transformed values for variables that were not normally distributed; the nonparametric Wilcoxon rank-sum test was used only when the log transformation was not sufficient to provide normally distributed data. Data are presented for non–log transformed values for ease of interpretation. Exercise levels were determined based on subjects' answer to the question, "On average, how often do you exercise?" taken from the University of Chicago Diabetes/Quality of Life Survey (20) and categorized as none (rarely), mild (once or twice a week), moderate (three times a week), and intense (more than three times a week). For confirmation of our analyses, we also performed multivariate regression analyses including all participants (n = 52) to characterize the associations between measures of OSA severity (i.e., AHI and arousal index) and the primary outcome variable, the insulin sensitivity index. Covariates used in these multivariable models included ethnicity-based diabetes risk, family history of diabetes, and fasting triglyceride levels. Partial correlation coefficients resulting from these confirmatory analyses are reported.

Statistical analyses were performed using JMP statistical software (version 9.0.2; SAS Institute) and Stata version 12 (StataCorp LP, College Station, TX). All reported P values are two sided with significance set at $P < 0.05$.

RESULTS—The demographic, cardiovascular, and sleep characteristics of all participants are presented in Table 1. The ethnic distribution of the entire cohort (n = 52) was as follows: 36 (69%) Caucasians, 8 (15%) African Americans, 6 (12%) Hispanics, and 2 (4%) Asians.

Twelve of 52 men had OSA. The severity of OSA was in the mild range (i.e., AHI <15) for all men except one individual who had moderate OSA and another individual who had severe OSA. Men with OSA and matched control subjects were similar in terms of age, BMI, ethnicity-based diabetes risk, family history of diabetes, and level of exercise (Table 1). Both groups had comparable average systolic and diastolic blood pressure and fasting triglyceride and LDL, HDL, and total cholesterol levels, which were all in the normal range according to clinical guidelines.

Total sleep time, sleep efficiency, and the amount of REM sleep did not differ significantly between men with OSA and control subjects. On average, the arousal index was significantly higher and the amount of slow-wave sleep (i.e., deep sleep) tended to be lower in those with OSA compared with control subjects, which is consistent with sleep fragmentation and poor sleep quality associated with OSA. Men with OSA had greater, but overall a mild degree of hypoxemia compared with control subjects, as reflected by a significantly higher oxygen desaturation index with an average minimum oxygen saturation of >90%.

The mean plasma glucose and insulin profiles during the OGTT for men with OSA and control men without OSA are

Table 1—*Demographic, cardiovascular, and sleep characteristics of participants*

	All men	Men with OSA	Control men without OSA	*P*†
n	52	12	20	
Age (years)	23.4 ± 0.4	23.9 ± 1.1	22.5 ± 0.6	0.21
BMI (kg/m^2)	22.6 ± 0.3	22.3 ± 0.5	22.6 ± 0.4	0.74
Ethnicity-based diabetes risk (high/low)	16/36	5/7	8/12	0.93
Family history of diabetes (yes/no)	5/47	3/9	2/18	0.34
Exercise level (none to mild/ moderate to intense)*	28/24	7/5	11/9	0.85
Epworth sleepiness score	5.1 ± 0.4	4.1 ± 0.6	5.0 ± 0.9	0.46
Cardiovascular**				
Systolic blood pressure (mmHg)	122.3 ± 1.5	120.7 ± 3.0	122.4 ± 2.4	0.67
Diastolic blood pressure (mmHg)	69.3 ± 1.2	67.0 ± 3.5	60.9 ± 2.2	0.46
Total cholesterol (mg/dL)	155.5 ± 4.9	158.9 ± 36.9	163.7 ± 7.8	0.72
LDL cholesterol (mg/dL)	88.5 ± 4.3	87.5 ± 9.8	95.0 ± 6.7	0.52
HDL cholesterol (mg/dL)	49.9 ± 1.6	53.5 ± 3.1	50.5 ± 2.7	0.47
Triglycerides (mg/dL)	85.4 ± 5.1	89.6 ± 12.5	90.8 ± 8.3	0.93
Polysomnography				
Total sleep time (min)	443.9 ± 6.0	446.2 ± 11.2	433.3 ± 10.0	0.41
Sleep efficiency (%)	87.2 ± 1.1	87.5 ± 2.3	85.0 ± 1.9	0.40
REM sleep (min)	100.7 ± 3.9	104.1 ± 10.2	99.4 ± 6.1	0.68
Slow-wave sleep (min)	58.2 ± 3.5	44.3 ± 9.5	61.4 ± 4.6	0.08
AHI (per hour of sleep)	3.9 ± 0.9	11.2 ± 2.9	1.6 ± 0.3	<0.0001
ODI (per hour of sleep)	0.8 ± 0.2	1.9 ± 0.9	0.3 ± 0.1	0.028
Minimum oxygen saturation (%)	91.4 ± 0.25	90.5 ± 0.45	92.3 ± 0.36	0.0040
Arousal index (per hour of sleep)	11.8 ± 1.0	19.1 ± 2.5	9.9 ± 1.1	0.0003

Data are means ± SEM unless otherwise specified. Control men without OSA (n = 20) were randomly selected from all controls (n = 40) by frequency-matching. Ethnicity-based diabetes risk was categorized as high for African Americans, Asians, and Hispanics and low for Whites. Family history of diabetes was considered positive if at least one first-degree relative had type 2 diabetes. Analyses were performed on log-transformed values for AHI and arousal index. †*P* values are for comparisons between men with OSA and control subjects and are from two-sided *t* tests for continuous variables and χ^2 tests for categorical variables except for oxygen desaturation index for 3% desaturation (ODI) (Wilcoxon rank-sum test) and family history of diabetes (Fisher exact test). *Exercise levels are from self-report (none, rarely; mild, once or twice a week; moderate, three times a week; and intense, more than three times a week) **Data are reported for blood pressure in n = 45 and for lipids in n = 43.

shown in Fig. 1. Measures of glucose tolerance, insulin sensitivity, and insulin secretion derived from the OGTT in all participants are shown in Table 2. Men with OSA had 27% lower insulin sensitivity (estimated by the Matsuda index) and 37% higher total insulin secretion (incAUC$_{ins}$) than the control subjects, whereas the glucose response (incAUC$_{glu}$) was not significantly different between the two groups (Table 2). The incAUC$_{ins}$/incAUC$_{glu}$, a measure of total insulin secretion, was significantly higher in men with OSA compared with control subjects, whereas early-phase insulin secretion (estimated by insulinogenic index [$I_{0–30}/G_{0–30}$]) was comparable between the two groups (Table 2). Fasting and 2-h insulin, fasting and 2-h glucose, HOMA-IR, and A1C levels did not differ significantly between men with OSA and control subjects (Table 2).

Multivariate regression models were used to further validate these findings through examination of associations between the indices of OSA severity (i.e., AHI and arousal index) and the primary outcome measure, the insulin sensitivity index (estimated by Matsuda index) in all participants (n = 52). After ethnicity-based diabetes risk and family history of diabetes were controlled for, both increasing AHI (partial correlation coefficient −0.37, P = 0.008) and arousal index (partial correlation coefficient −0.38, P = 0.006) were strongly associated with decreasing insulin sensitivity, whereas no correlation was found between the insulin sensitivity index and oxygen desaturation index (P = 0.809).

CONCLUSIONS—In this study, we demonstrate for the first time that in young lean men (mean age <24 years; mean BMI <23 kg/m^2) who are otherwise healthy and free of cardiometabolic disease, the presence of OSA is associated with insulin resistance and compensatory hyperinsulinemia to maintain normal glucose homeostasis. Men with OSA had 27% lower insulin sensitivity accompanied by a 37% higher total insulin secretion after ingestion of glucose load compared with control men of similar age, BMI, ethnicity-based diabetes risk, family history of diabetes, exercise habits, blood pressure, and fasting lipids levels. These findings are in agreement with previous work supporting associations between OSA and insulin resistance and type 2 diabetes in overweight and obese populations (5,6,11). Importantly, our findings provide evidence to support the hypothesis that OSA may adversely affect glucose metabolism at a very young age even in the absence of obesity, cardiovascular disease, and other known risk factors for type 2 diabetes.

We did not detect any significant difference in fasting glucose and insulin levels between men with OSA and control subjects. The HOMA-IR based on fasting glucose and insulin levels was not significantly different between the two groups. In contrast, three previous studies conducted in lean Asian individuals (8–10) have found associations between the presence and severity of OSA and HOMA-IR. In contrast to our young and healthy cohort, the patients included in these prior studies were middle-aged patients with symptoms of OSA (e.g., snoring, witnessed apneas, daytime sleepiness) who were selected from sleep disorder clinics and were taking medications to treat comorbid conditions including hypertension, dyslipidemia, and type 2 diabetes. In agreement with our findings, in the Sleep Heart Health Study (11), a large community-based cohort of older individuals (~50% >65 years of age), the presence of OSA was associated with a higher prevalence of prediabetes and occult diabetes in the nonoverweight group (n = 370, BMI <25 kg/m^2). Our result showing that even a mild degree of OSA

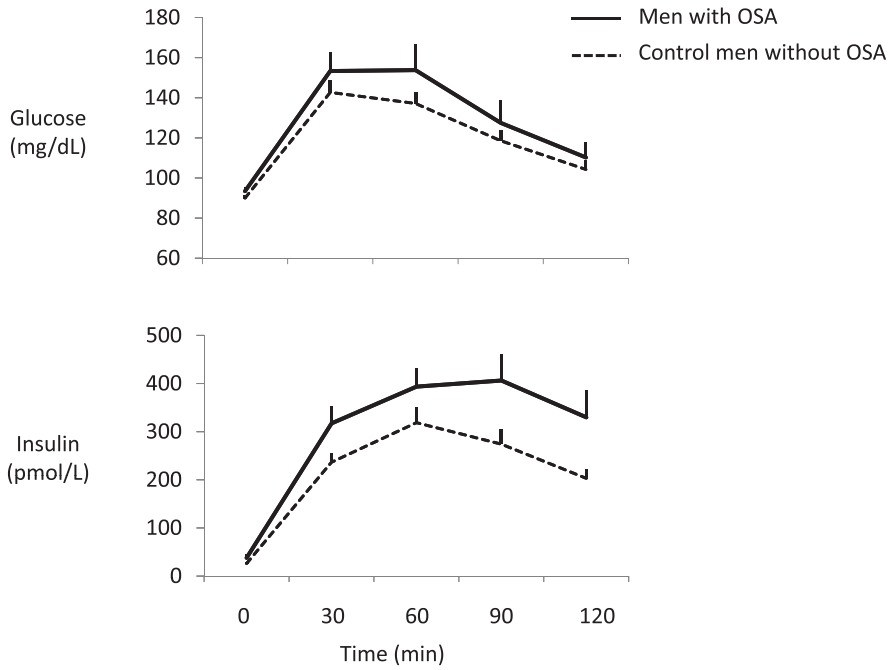

Figure 1—*Mean plasma glucose and insulin profiles during the OGTT.*

is associated with insulin resistance in otherwise healthy men is consistent with findings from a larger study that included 118 nondiabetic subjects with no significant comorbidities and demonstrated that increasing severity of OSA is associated with greater insulin resistance (estimated by intravenous glucose tolerance test) after statistical adjustments for age, sex, race, and percent body fat (6).

In our study, subjects were not selected according to sleep complaints or symptoms of OSA, and the overall presence of OSA was 23% (12 of 52 subjects with OSA), which appears to be higher than expected for a young lean population based on prior population studies (3,18,21). This comparison could be misleading, and the overall presence of OSA in our study should be interpreted with caution for several reasons. First, our study was not designed to explore the prevalence of OSA using a random or systematic sample from the population and thus may not provide the true prevalence estimates in young lean individuals. Second, we believe that our small sample size further limits the ability to make reasonable prevalence calculations. Third, compared with prior population-based studies, our overall high presence of OSA could be partly explained by important differences in the techniques used to detect respiratory events as well as the scoring criteria. The prior population studies have all used the thermistor as the nasal airflow sensor to detect respiratory events. In contrast, in our study the airflow was monitored using a more sensitive method (i.e., the nasal pressure transducer) in addition to the thermistor. In the population-based cohorts, hypopneas were defined using strict criteria of a reduction in airflow accompanied by a ≥4% oxygen desaturation, without consideration for the presence of arousals. In contrast, we used less stringent criteria for detecting hypopneas, which include a reduction in airflow associated with either a ≥3% desaturation or an arousal, as defined in the most current American Academy of Sleep Medicine scoring guidelines (13). Of note, when we have rescored our data using a more strict definition of hypopneas based only on a minimum of 4% desaturation (without considering the arousals), only 2 of the 52 subjects (3.8%) were categorized as having OSA (AHI >5), which suggests that using only oxygen criteria, the presence of OSA may not be captured in young lean populations. Indeed, there is evidence to suggest that different scoring criteria used for determining the AHI contribute to substantial variability in identification and classification of OSA status (19,22). In particular, there is also evidence to support the clinical relevance of arousals and the importance of arousal-based criteria for hypopnea definition in lean patients with OSA (23).

The respiratory disturbances in OSA are typically associated with intermittent hypoxia and transient arousals, which may alter glucose metabolism through multiple pathways including activation of the sympathetic nervous system, dysregulation of the hypothalamic-pituitary

Table 2—*Measures of glucose tolerance, insulin sensitivity, and insulin secretion*

	All men	Men with OSA	Control men without OSA	*P*†
n	52	12	20	
A1C (%)*	5.3 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	0.56
Fasting glucose (mg/dL)	90.3 ± 0.9	93.4 ± 1.8	90.0 ± 1.6	0.18
2-h glucose (mg/dL)	100.2 ± 3.3	110.2 ± 7.7	104.2 ± 4.6	0.48
Fasting insulin (pmol/L)	28.5 ± 2.2	37.9 ± 6.4	26.2 ± 3.0	0.12
2-h insulin (pmol/L)	224.7 ± 22.0	329.8 ± 57.1	203.1 ± 19.8	0.10
$incAUC_{glu}$ ($\mu U \cdot mL^{-1} \cdot min$)	9,315.0 ± 377.0	10,486.9 ± 1,050.0	9,464.3 ± 489.4	0.42
$incAUC_{ins}$ ($mg \cdot dL^{-1} \cdot min$)	3,920.3 ± 225.6	4,781.7 ± 475.8	3,492.2 ± 310.9	0.024
$incAUC_{ins}/incAUC_{glu}$	0.43 ± 0.02	0.47 ± 0.04	0.37 ± 0.03	0.048
HOMA-IR	8.9 ± 0.7	12.4 ± 2.2	8.1 ± 1.0	0.21
Matsuda index	10.5 ± 0.6	8.1 ± 1.4	10.9 ± 0.8	0.021
$I_{0–30}/G_{0–30}$ (pmol/mmol)	96.4 ± 6.0	95.0 ± 13.8	83.0 ± 8.3	0.44

Data are means ± SEM unless otherwise indicated. Control men without OSA (n = 20) were randomly selected from all controls (n = 40) by frequency-matching. †*P* values are for comparisons between men with OSA and control subjects and are from two-sided t tests for continuous variables except for HOMA-IR (Wilcoxon rank-sum test). *Data are reported for A1C in n = 45. Analyses were performed on log-transformed values for fasting insulin, 2-h insulin, $incAUC_{glu}$, HOMA-IR, and Matsuda index.

axis, and systemic inflammation (24–29). In our sample, the severity of OSA was overall in the mild range, and the respiratory events were mostly associated with arousals rather than severe oxygen desaturations, which in turn resulted in increased sleep fragmentation and reduced amount of deep slow-wave sleep. Consistent with our findings, two experimental studies in healthy young adults that used acoustic stimuli to induce sleep fragmentation and suppression of deep slow-wave sleep found a ~25% decrease in insulin sensitivity (30,31). In both studies, sleep fragmentation resulted in increased sympathetic activity estimated by spectral analysis of heart rate variability, which could potentially explain the insulin resistance observed after experimental manipulations of sleep quality. There is also evidence that intermittent hypoxia induced in healthy humans results in elevated blood pressure, increased sympathetic activity, and decreased insulin sensitivity (32–34). In animal models of OSA, intermittent hypoxia and subsequent sleep fragmentation result in sympathetic activation, impaired glucose homeostasis, and insulin resistance (35). Taken together, evidence from both animal and human models that mimic OSA supports a potential causal role for OSA in insulin resistance.

This study has several limitations. Our sample size was relatively small due to highly selective eligibility criteria, and we used indirect OGTT-based measures of insulin sensitivity and secretion. We did not collect objective data on physical activity and dietary habits, which could be residual confounders. Nevertheless, self-reported exercise levels were similar between men with OSA and control subjects. Differences in fat distribution, particularly visceral fat, which were not assessed in our study, may explain some of the association between the presence of OSA and altered insulin sensitivity and secretion. Specifically, we did not quantify abdominal fat by imaging techniques or collect data on waist circumference, which represents a potential limitation of our study. It should be noted, however, that simply measuring waist-to-hip ratio may not be a good predictor of central obesity in this group of lean men, since the recommended waist circumference thresholds for increased cardiometabolic risk in men identify only 1% of men with "high" waist circumference and normal BMI (36). It has been proposed that an elevated fasting triglyceride level can be used as a marker of excess visceral adipose tissue storage and related metabolic abnormalities in otherwise healthy individuals (37). In our sample, the fasting triglyceride levels were not elevated and there was not a significant difference in triglyceride levels between men with OSA and control subjects. In an exploratory analysis of our dataset, when triglyceride levels were added to the regression model (after use of multiple imputation methods to impute missing triglyceride values for nine men) that included ethnicity-based diabetes risk and family history of diabetes as covariates, the relationship between AHI and insulin sensitivity index remained significant ($P = 0.015$). Our study only included men, and it is conceivable that there may be a differential effect of OSA on insulin sensitivity and secretion in women given the known sex disparities in body fat distribution. Further research on OSA and glucose metabolism taking sex differences into consideration would be worthwhile. We report no significant difference in subjective daytime sleepiness (as assessed by the Epworth Sleepiness Scale) between those with OSA and the control subjects, but we did not collect data on objective sleepiness or any other OSA symptoms such as snoring, witnessed apneas, etc. The diagnosis of OSA in our young, lean, and otherwise healthy subjects was based on a single night of sleep recording in the laboratory, and we did not measure our subjects' sleep patterns at home. However, our findings on glucose metabolism after ingestion of glucose load in the laboratory setting are entirely compatible with the well-documented natural history of type 2 diabetes, where the early stages involve normal glycemia associated with insulin resistance and compensatory hyperinsulinemia (38). More research will be needed to address the question of whether the changes in insulin secretion and action that we observed in these young and lean men with OSA may lead to earlier impaired glucose tolerance or frank diabetes in the long term, particularly when these individuals grow older and gain more weight.

In summary, our results demonstrate that in a unique population of very young, lean, and healthy men who are free of cardiometabolic disease, the presence of OSA is associated with insulin resistance and a compensatory rise in insulin secretion to maintain normal glucose tolerance after ingestion of glucose load. These findings have important clinical implications as they suggest that the presence of OSA, in the absence of increased adiposity or other cardiometabolic risk factors, may promote the development of type 2 diabetes in men. Future large-scale controlled studies are needed to assess whether rigorous screening for and early treatment of OSA may reverse insulin resistance and prevent high-risk individuals from progressing to a diabetic state.

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S.P. reviewed, analyzed, and interpreted data; wrote the manuscript; and had final approval of the version to be published. K.W. analyzed and performed statistical interpretation of data, revised the manuscript, and had final approval of the version to be published. J.B., A.D., E.C.H., and V.A. acquired data, revised the manuscript, and had final approval of the version to be published. E.T. conceived and designed the study; acquired, reviewed, analyzed, and interpreted data; wrote the manuscript; and had final approval of the version to be published. E.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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